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MUELLER AND SMITH, LPA
MUELLER-SMITH BUILDING
7700 RIVERS EDGE DRIVE
COLUMBUS, OH 43235

EXAMINER	
ANDERSON, JAMES D	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/807,620
Filing Date: March 24, 2004
Appellant(s): AU ET AL.

Jerry K. Mueller, Jr.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/7/2010 appealing from the Office action mailed 4/19/2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 27, 28, 32, 33, and 35.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

6,900,235	Agyin et al.	5-2005
5,597,830	Klohs et al.	1-1997

Tu et al. "Phase I Study of Suramin Combined with Doxorubicin in the Treatment of Androgen-independent Prostate Cancer" Clinical Cancer Research, vol. 4, May 1998, pages 1193-1201

Lopez et al. "The Synergistic and Antagonistic Effects of Cytotoxic and Biological Agents on the In Vitro Antitumor Effects of Suramin" European Journal of Cancer, vol. 30A, no. 10, 1994, pages 1545-1549

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-28, 32-33, and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Appellant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. This is a New Matter rejection.

The claims are drawn to a kit comprising “not substantially in excess of about 800 mg of suramin" formulated in a pharmaceutical carrier.

There is no support, either explicit or implicit, for the claimed amount of suramin. Nowhere do Appellants teach the claimed limitation of an amount of suramin "not substantially in excess of about 800 mg” present in a kit.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Appellant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are now drawn to a kit comprising “not substantially in excess of about 800 mg of suramin" formulated in a pharmaceutical carrier.

There is no disclosure of such an amount of suramin in the instant application.

Appellant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Appellant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-28, 32-33, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Agyin et al**. (USP No. 6,900,235; Issued May 31, 2005; Filed Sep. 29, 2000).

Agyin et al. disclose benzimidazole compounds for the treatment of cancers (Abstract; col. 2, line 39 to col. 3, line 61). The benzimidazole compounds are inhibitors of microtubules as recited in claim 22 (col. 25, lines 43-67; Table 5). The compounds of the invention are disclosed to be useful in combination therapy, such as by combining the benzimidazole compound with a chemotherapeutic agent and/or "potentiator" (col. 17, lines 1-60; col. 23, lines 29-31). A suitable potentiator is suramin as recited in claim 35 (col. 17, lines 56-57).

Agyin et al. disclose pharmaceutical kits for the treatment of cancer comprising one or more containers containing a pharmaceutical composition comprising a compound of the invention, pharmaceutically acceptable carriers, and instructions, e.g., printed instructions either

as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components (col. 24, lines 7-22).

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art to formulate a kit comprising suramin as a potentiator and an anti-microtubule agent as disclosed in Agyin et al. for the treatment of cancer. One skilled in the art would have been motivated to additionally provide instructions for the therapeutic use of a suramin potentiator in combination with an anti-microtubule agent of Agyin et al. As discussed in previous Office Actions, there must be a functional relationship between the printed matter and a substrate in order for printed material to have any patentable weight.

With regard to claims 27-28 and 32-33, in view of the guidance provided in the MPEP and the court decisions in Gulack and especially Ngai, it is the position of the Examiner that the instantly claimed instructions for using suramin in combination with cytotoxic agents do not provide a functional relationship between the printed matter and the claimed product and thus are not given patentable weight. All the printed matter does is teach how to administer suramin to achieve a circulating concentration of below about 200 μM in a patient. Claim 27-28 and 32-33 only characterize the concentration of suramin that would result from administration of suramin according to the nomogram in claim 35.

Claims 27-28, 32-33, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Tu et al**. (Clinical Cancer Research, May 1998, vol. 4, pages 1193-1201) in view of **Agyin et al**. (USP No. 6,900,235; Issued May 31, 2005; Filed Sep. 29, 2000).

Tu et al. disclose that suramin combined with doxorubicin is effective in the treatment of patients with androgen-independent prostate cancer (Abstract). The authors disclose that suramin is an agent with diverse biological effects that result in tumor suppression with cytotoxic effects including activation of apoptotic cell death, inhibition of cellular energy metabolism, and inhibition of DNA and RNA polymerases, protein kinase C, and DNA topoisomerase II (page 1193, right column). The most serious toxicities of suramin are dose dependent and occur when plasma suramin levels exceed 350 μg/mL.[1] Suramin was known to have synergistic antitumor

[1] The molecular weight of suramin is 1429.21 g/mol. 350 μg/mL is equivalent to about 245 μM.

activity when combined with doxorubicin (page 1193, right column). Doxorubicin is an antitumor antibiotic whose mechanism of action is believed to involve the formation of free radicals and the inhibition of topoisomerase II, causing DNA damage (id.).

The authors provide instructions for administering suramin and doxorubicin to patients to treat prostate cancer and provide measurements of suramin plasma concentrations (pages 1194-1195; Table 3). Tu et al. specifically disclose adjusting suramin doses proportionately based on assessment of steady-state plasma concentrations of suramin (page 1194, right column). As seen in Table 3, the circulating plasma concentrations of suramin are below about 200 μM as recited in the instantly claimed instructions. In fact, the authors disclose that single-agent suramin has a narrow clinical therapeutic index of 150 to 250 μg/mL (page 1199, left column). 150 to 250 μg/mL suramin is equivalent to 105 to 175 μM suramin, which is below the amount recited in the claimed instructions.

The authors conclude that the results from this study could be used to develop future clinical studies of suramin combined with other chemotherapeutic agents in the treatment of prostate cancer and that long-term exposure to suramin at lower concentrations and in combination with other chemotherapeutic agents should be explored. The authors explicitly suggest a fixed dosing scheme targeting a suramin concentration of 200 μg/mL (i.e., 140 μM) for future suramin combination studies (page 1200, right column).

Tu et al. differ from the instant claims in that they do not explicitly disclose a "kit" comprising suramin and doxorubicin and instructions for administration.

However, providing therapeutically active agents in kits with instructions for administration of the active agents is routine in the art of medicine. The skilled artisan is aware of the benefits of such kits, such as ease of transport, storage, and distribution. For example, Agyin et al. disclose pharmaceutical kits for the treatment of cancer comprising one or more containers containing a pharmaceutical composition comprising a compound of the invention, pharmaceutically acceptable carriers, and instructions, e.g., printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components (col. 24, lines 7-22).

As such, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate a kit comprising suramin and doxorubicin as suggested and motivated by Tu et al. for use in the treatment of prostate cancer. Using the disclosure of Tu et al. as a guide, the skilled artisan could readily provide instructions for administering suramin and doxorubicin to treat prostate cancer, wherein the dose of suramin administered is such that a therapeutic, non-toxic concentration of suramin is provided to the patient. Tu et al. disclose that single-agent suramin has a narrow clinical therapeutic index of 150 to 250 μg/mL (i.e., 105 to 175 μM) and explicitly suggest a fixed dosing scheme targeting a suramin concentration of 200 μg/mL (i.e., 140 μM). Agyin et al. disclose that it is well-known and routine in the art to provide therapeutic agents in pharmaceutical kits comprising a therapeutic agent(s), pharmaceutically acceptable carriers, and instructions, e.g., printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components.

With regard to claims 27-28 and 32-33, in view of the guidance provided in the MPEP and the court decisions in Gulack and especially Ngai, it is the position of the Examiner that the instantly claimed instructions for using suramin in combination with cytotoxic agents do not provide a functional relationship between the printed matter and the claimed product and thus are not given patentable weight. All the printed matter does is teach how to administer suramin to achieve a circulating concentration of below about 200 μM in a patient. Claim 27-28 and 32-33 only characterize the concentration of suramin that would result from administration of suramin according to the nomogram in claim 35. Regardless of this fact, as discussed above, Tu et al. provide guidance and direction to administer suramin in such a way so as to provide a circulating concentration of suramin below 200 μM.

Claims 27-28, 32-33, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Klohs et al**. (USP No. 5,597,830; Issued Jan. 28, 1997) in view of **Agyin et al**. (USP No. 6,900,235; Issued May 31, 2005; Filed Sep. 29, 2000).

Klohs et al. disclose suramin in combination with a vinca alkaloid or estramustine is synergistic for treating cancer (Abstract). Compositions for use in the invention consist

essentially of suramin and a vinca alkaloid or estramustine together with common excipients, diluents, and carriers (col. 1, line 65 to col. 2, line 10). Suramin is disclosed to be administered at doses from about 275 mg/m^2 to about 1000 mg/m^2 and ideally is administered at a dose to provide plasma levels of about 100 to about 300 μg/mL (i.e., about 70 μM to about 210 μM) (col. 2, lines 27-35). The inventors disclose a combination comprising each active ingredient packaged separately, wherein the individually packaged drugs can be placed in a single carton, thereby providing convenience to the attending physician or medical attendant (i.e., a kit) (col. 4, lines 39-44).

Klohs et al. differ from the instant claims in that they do not explicitly disclose a kit comprising suramin and a vinca alkaloid or estramustine and instructions for administration.

However, providing therapeutically active agents in kits with instructions for administration of the active agents is routine in the art of medicine. The skilled artisan is aware of the benefits of such kits, such as ease of transport, storage, and distribution. Klohs et al. disclose that kits comprising the individual active agents provide convenience to physicians or medical attendants. Agyin et al. disclose pharmaceutical kits for the treatment of cancer comprising one or more containers containing a pharmaceutical composition comprising a compound of the invention, pharmaceutically acceptable carriers, and instructions, e.g., printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components (col. 24, lines 7-22).

As such, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate a kit comprising suramin and a vinca alkaloid or estramustine as suggested and motivated by Klohs et al. for use in the treatment of cancer. Using the disclosure of Klohs et al. as a guide, the skilled artisan could readily provide instructions for administering suramin and a vinca alkaloid or estramustine to treat cancer, wherein the dose of suramin administered is such that a therapeutic, non-toxic concentration of suramin is provided to the patient. Klohs et al. disclose that suramin is to be administered at doses from about 275 mg/m^2 to about 1000 mg/m^2 and ideally is administered at a dose to provide plasma levels of about 100 to about 300 μg/mL (i.e., about 70 μM to about 210 μM)

(col. 2, lines 27-35). The inventors disclose a kit comprising each active ingredient packaged separately wherein the individual packages can be placed in a single carton. Agyin et al. disclose that it is well-known and routine in the art to provide therapeutic agents in pharmaceutical kits comprising a therapeutic agent(s), pharmaceutically acceptable carriers, and instructions, e.g., printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components.

With regard to claims 27-28 and 32-34, in view of the guidance provided in the MPEP and the court decisions in Gulack and especially Ngai, it is the position of the Examiner that the instantly claimed instructions for using suramin in combination with cytotoxic agents do not provide a functional relationship between the printed matter and the claimed product and thus are not given patentable weight. All the printed matter does is teach how to administer suramin to achieve a circulating concentration of below about 200 μM in a patient. Claim 27-28 and 32-33 only characterize the concentration of suramin that would result from administration of suramin according to the nomogram in claim 35. Regardless of this fact, as discussed above, Klohs et al. provide guidance and direction to administer suramin in such a way so as to provide suramin plasma levels of about 100 to about 300 μg/mL (i.e., about 70 μM to about 210 μM).

Claims 27-28, 32-33, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Lopez et al**. (European Journal of Cancer, 1994, vol. 30A, no. 10, pages 1545-1549) in view of **Klohs et al**. (USP No. 5,597,830; Issued Jan. 28, 1997) and **Agyin et al**. (USP No. 6,900,235; Issued May 31, 2005; Filed Sep. 29, 2000).

Lopez et al. disclose that suramin has shown antitumor activity in vitro and in vivo and that at plasma levels higher than 200 μM there is excessive toxicity (Abstract). Lopez et al. sought to improve the antitumor effects of suramin by combining it with several other antitumor agents. In this regard, the authors demonstrate that suramin in combination with doxorubicin, 5-fluorouracil, cisplatin, or tumor necrosis factor resulted in synergistic growth inhibition of breast and/or prostate cancer cells (Abstract; Table 2).

The instant claims differ from Lopez et al. in that the primary reference does not disclose kits comprising suramin.

However, Klohs et al. disclose suramin in combination with a vinca alkaloid or estramustine is synergistic for treating cancer (Abstract). Suramin is disclosed to be administered at doses from about 275 mg/m^2 to about 1000 mg/m^2 and ideally is administered at a dose to provide plasma levels of about 100 to about 300 μg/mL (i.e., about 70 μM to about 210 μM) (col. 2, lines 27-35). The inventors disclose a combination comprising each active ingredient packaged separately, wherein the individually packaged drugs can be placed in a single carton, thereby providing convenience to the attending physician or medical attendant (i.e., a kit) (col. 4, lines 39-44).

The instant claims differ from Klohs et al. in that the secondary reference does not teach kits with instructions for administration.

However, providing therapeutically active agents in kits with instructions for administration of the active agents is routine in the art of medicine. The skilled artisan is aware of the benefits of such kits, such as ease of transport, storage, and distribution. Klohs et al. disclose that kits comprising the individual active agents (e.g., suramin and a cytotoxic agent) provide convenience to physicians or medical attendants. Agyin et al. disclose pharmaceutical kits for the treatment of cancer comprising one or more containers containing a pharmaceutical composition comprising a compound of the invention, pharmaceutically acceptable carriers, and instructions, e.g., printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components (col. 24, lines 7-22).

As such, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate a kit comprising suramin and doxorubicin, 5-fluorouracil, cisplatin, or tumor necrosis factor as suggested and motivated by Lopez et al. in view of Klohs et al. for use in the treatment of cancer. Using the disclosures of Lopez et al. and Klohs et al. as a guide, the skilled artisan could readily provide instructions for administering suramin and doxorubicin, 5-fluorouracil, cisplatin, or tumor necrosis factor to treat cancer, wherein the dose of suramin administered is such that a therapeutic, non-toxic concentration of suramin is provided to the patient. Lopez et al. teach that plasma levels above 200 μM, suramin results in "excessive toxicity", thus motivating one skilled in the art to administer suramin in

doses so as not to exceed a plasma level above 200 μM. Klohs et al. provide such guidance, disclosing that suramin is to be administered at doses from about 275 mg/m^2 to about 1000 mg/m^2 and ideally is administered at a dose to provide plasma levels of about 100 to about 300 μg/mL (i.e., about 70 μM to about 210 μM) (col. 2, lines 27-35). Klohs et al. disclose a kit comprising each active ingredient packaged separately wherein the individual packages can be placed in a single carton. The skilled artisan could readily and routinely modify the kits of Klohs et al. so as to provide kits comprising suramin and other cytotoxic agents, such as doxorubicin, 5-fluorouracil, cisplatin, or tumor necrosis factor as suggested and motivated by Lopez et al. Agyin et al. disclose that it is well-known and routine in the art to provide therapeutic agents in pharmaceutical kits comprising a therapeutic agent(s), pharmaceutically acceptable carriers, and instructions, e.g., printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components.

With regard to claims 27-28 and 32-33, in view of the guidance provided in the MPEP and the court decisions in Gulack and especially Ngai, it is the position of the Examiner that the instantly claimed instructions for using suramin in combination with cytotoxic agents do not provide a functional relationship between the printed matter and the claimed product and thus are not given patentable weight. All the printed matter does is teach how to administer suramin to achieve a circulating concentration of below about 200 μM in a patient. Claim 27-28 and 32-33 only characterize the concentration of suramin that would result from administration of suramin according to the nomogram in claim 35. Regardless of this fact, as discussed above, both Lopez et al. and Klohs et al. provide guidance and direction to administer suramin in such a way so as to provide suramin plasma levels of below about 200 μM (Lopez et al.) or about 100 to about 300 μg/mL (i.e., about 70 μM to about 210 μM) (Klohs et al.).

Regarding the above rejections under 35 U.S.C. 103, it is noted that the MPEP and established case law supports the rejection of pharmaceutical kits that differ from the prior art only in the content of the provided instructions. The following section of the M.P.E.P., as noted by Appellants in their response filed 9/10/2007 (page 7) is deemed relevant to the present claims:

> "Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. In re Ngai, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004) (Claim at issue was a kit requiring instructions and a buffer agent. The Federal Circuit held that the claim was anticipated by a prior art reference that taught a kit that included instructions and a buffer agent, even though the content of the instructions differed.). See also In re Gulack, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed. Cir. 1983) ("Where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability .... [T]he critical question is whether there exists any new and unobvious functional relationship between the printed matter and the substrate.")." M.P.E.P. § 2112.01

The decision in Gulack held that there must be a functional relationship between the printed matter and a substrate in order for printed material to have any patentable weight. However, in Ngai, the court distinguished claims directed to a kit comprising instructions and a buffer (more closely related to the present case) from the printed band and instructions at issue in Gulack. There the printed matter and the circularity of the band were interrelated, so as to produce a new product useful for "educational and recreational mathematical" purposes. In Ngai, addition of a new set of instructions into a known kit was held to not interrelate with the kit in the same way as the numbers interrelated with the band. In Gulack, the printed matter would not achieve its educational purposes without the band, and the band without the printed matter would similarly be unable to produce the desired result. In the present case, the printed matter in no way depends on the kit (i.e., a kit containing suramin formulated in a pharmaceutical carrier), and the kit does not depend on the printed matter (i.e., instructions for administering suramin). All that the printed matter does is teach a method of administering an obvious product. As the court stated in Ngai, "If we were to adopt Ngai's position, anyone could continue patenting a product indefinitely provided that they add a new instruction sheet to the product. This was not envisioned by Gulack. Ngai is entitled to patent his invention of a new RNA extraction method, and the claims covering that invention were properly allowed. He is not, however, entitled to patent a known product by simply attaching a set of instructions to that product." (Emphasis added).

In the instant case, the cited prior art clearly teaches, suggests, and motivates one skilled in the art to formulate pharmaceutical compositions and kits comprising suramin and other

cytotoxic agents for the treatment of cancer. It was clearly known in the art that suramin has antitumor activity, is synergistic when combined with other chemotherapeutic agents, and results in excessive toxicity when plasma levels of suramin are greater than 200 μM. As such, it would be obvious to one skilled in the art to formulate suramin in a kit with other cytotoxic agents, especially those which were known to be synergistic when administered with suramin, and to provide instructions for treating cancer with the active agents in the kit. It would further have been obvious to the skilled artisan to instruct those administering suramin not to administer doses that result in plasma concentrations above 200 μM which cause excessive toxicity. As discussed above, the claimed instructions do not control what is in the kit. Put another way, the recited instructions have no bearing and place no limitations on the components of the kit, the content of the kit, or the amounts of active agents in the kit. The kit, in and of itself, stands alone and does not require the claimed instructions to "breath life and meaning" into the kit. Rather, the instructions only tell one skilled in the art how to administer the components of the kit in a particular manner. As such, there is not a functional relationship between the instructions and the claimed kit.

There can be no doubt that the skilled artisan could administer suramin and a cytotoxic agent in a manner distinct from that disclosed in Appellant's recited instructions. However, even such a distinct administration method does not change the contents of the kit or the amounts of active agents present in the kit.

(10) Response to Argument

Appellant's arguments filed 10/7/2010 have been fully considered but they are not persuasive.

With regard to the 35 U.S.C. 112, 1st Paragraph rejection (New Matter) of claims 27-28, 32-33, and 35, Appellants argue that a vial of suramin containing up to 800 mg would "then be a logical choice". See Brief at page 24. Appellants appear to be arguing that because the disclosure discloses administering suramin in a required dose to establish a low circulating

concentration in a patient of below about 200 μM and because using the disclosed nomogram to calculate a dose for a patient with a body surface area of 2.5 m^2 would provide a required dose of 781 mg, the specification provides written support for the claimed composition comprising not substantially in excess of about 800 mg. In response, the Examiner respectfully submits that nowhere in the disclosure do Appellants disclose amounts of suramin intended to be present in the claimed compositions. The disclosed nomogram is used to calculate a dose of suramin to administer to a patient, not an amount of suramin to be present in a kit.

With regard to the 35 U.S.C. 103 rejections of claims 27-28, 32-33, and 35, Appellants make the following arguments, which are addressed by the Examiner below. For ease of discussion, Appellants' arguments are sequentially numbered in the order present by Appellants at pages 13-23 of the Appeal Brief.

I. Appellants argue that the printed instructions provide a new and unobvious functional relationship between the nomogram and the administration of non-cytotoxic suramin as a sensitizer (Brief at page 15).

The issue of the claimed printed instructions has been discussed in the prosecution of the instant application. It is the position of the Examiner in view of established case law that because the cited prior art teaches, suggests, and motivates providing suramin in a kit with instructions for administration to a patient, the content of the printed instructions does not distinguish Appellants' kit from that suggested by the prior art. Appellants' printed instructions only affect how suramin is administered to a patient - they have no bearing whatsoever on the contents of the kit or the amounts present in the kit.

II. Appellants argue that it is material error to "ignore" printed instructions in applying Section 103(a), even if the printed matter does not constitute patentable subject matter.

Respectfully, the Examiner has not "ignored" the printed instructions. Rather, the Examiner maintains that the content of the claimed printed instructions is not a patentable distinction.

III. Appellants argue that the claimed kit provides a new and unobvious functional relationship between suramin and the printed instructions in so far as the printed instructions inform the user that a patient must have a low dose of circulating suramin over the duration of 48 hours and provide an algorithm and the associated nomogram table for the physician or pharmacist to use to calculate the proper dose of non-cytotoxic suramin for each patient based on criteria not taught by Agyin, Tu, Klohs, or any other reference.

The Examiner does not dispute that Appellants have discovered a method of calculating a dose of suramin to administer to a patient. However, the claims under appeal do not recite a method of calculating a dose of suramin or a method of administering suramin. The appealed claims are drawn to an obvious product.

IV. Appellants argue that their disclosure of the nomogram is based on unexpected and surprising findings made after substantial experimentations in experimental animals and in human patients. Appellants argue that absent the dosing nomogram in the instant disclosure, it will be impossible to predict how an individual patient will react to the administered dose of suramin and it will be impossible to calculate the correct dose based on the art of dose calculation for other drugs or cytotoxic suramin.

Appellants' examples are directed to methods of calculating a dose of suramin and methods of administering suramin to patient, not to kits comprising suramin. The claimed kit stands alone, whether the nomogram is present or not, i.e., the contents of the kit do not depend on the nomogram. Likewise, calculating a dose of suramin to administer to a patient does not need the claimed kit, i.e., any kit comprising suramin in a carrier would benefit from a nomogram directing the physician how much suramin to administer.

V. Appellants argue that the nomogram disclosed in the printed instructions is a novel method developed after extensive research undertaken to overcome or correct the deficiencies or misunderstanding in the art. In this regard, Appellants argue that the ability to use non-cytotoxic suramin as a sensitizer in patients relies on using the printed instructions for nomogram for dose calculation. Appellants assert that the suramin in the kit cannot be used to provide a personalized treatment to a patient in accordance to said patient's characteristics without the printed matter. Likewise, Appellants argue, the intended use of the printed instructions can only be practiced when the suramin is contained in the same kit.

If Appellants were claiming a method of administering suramin to a patient by calculating a dose of suramin to administer to a subject using the disclosed nomogram, the claims would likely be free of the prior art. However, Appellants are not claiming a method, they are claiming a product. Suramin in a kit/composition can be used without the recited nomogram, i.e., the skilled artisan could administer suramin to a patient using doses already known in the art. Or, one skilled in the art could calculate the dose of suramin using a different nomogram or different calculation. Likewise, the printed instructions do not require the

particular kit recited in the instant claims. Any kit or composition comprising suramin could be used with the disclosed printed instructions.

VI. Appellants argue that the nomogram in effect is "transforming suramin from a compound with no therapeutic value to a potentially useful drug".

This is not persuasive because suramin was already known in the art to be an effective drug as evidenced by the cited prior art. As such, it would be obvious to formulate suramin in a kit with instructions for administration as discussed in the 35 U.S.C. 103 rejections set forth supra. That Appellants have determined a calculation for optimizing the dose of suramin to administer to a patient does not negate the fact that kits and compositions comprising suramin are suggested and motivated by the cited prior art.

VII. Appellants argue that Agyin does not disclose a kit with suramin, instructions, and another chemotherapeutic. However, Appellants also state, "...Agyin discloses pharmaceutical kits and, due to the broad description of kits in Agyin, such kits could even contain suramin" (emphasis added). See page 18 of Brief. Appellants argue that the kit of the instant disclosure is not obvious over Agyin as the printed matter, including the dosing nomogram, is functionally related to the substrate of the kit (suramin), and has a new and unobvious relationship to the substrate. This is not persuasive for the reasons discussed supra, i.e., the issue of the claimed printed instructions has been discussed in the prosecution of the instant application and it is the position of the Examiner in view of established case law that because the cited prior art teaches, suggests, and motivates providing suramin in a kit with instructions for administration to a patient, the content of the printed instructions does not distinguish Appellants' kit from that suggested by the prior art. Appellants' printed instructions only affect how suramin is

administered to a patient - they have no bearing whatsoever on the contents of the kit or the amounts present in the kit.

VIII. Appellants argue that Agyin does not teach a suramin combination and does not teach suramin as a potentiator.

This is not persuasive because Agyin et al. disclose benzimidazole inhibitors of microtubules for the treatment of cancers that are useful in combination therapy, such as by combining the benzimidazole compound with a chemotherapeutic agent and/or "potentiator" (col. 17, lines 1-60; col. 23, lines 29-31). A suitable potentiator is suramin as recited in claim 35 (col. 17, lines 56-57). Accordingly, Appellants argument that Agyin does not teach suramin as a potentiator is without merit.

IX. Appellants attack the teachings of Agyin, stating that Agyin provides limited data to support enablement for the treatment of cancers. In support of this argument, Appellants argue that Agyin provides cytotoxicity data for 43 benzimidazole compounds in vitro but none of these compounds showed in vivo antitumor effects at the highest dose tested.

This argument is not persuasive because as admitted by Appellants, Agyin demonstrates that compound 3-1 shows a T/C value of 132% at 50 mg/kg administered i.p. That other doses showed lower T/C values is not demonstrative that Agyin is not enabled.

X. Appellants argue that Agyin does not teach a suramin combination while at the same time admitting that Agyin proposes to use the benzimidazoles in combination with any chemotherapeutic agent. See Brief at page 19. Appellants argue that the number of possible combinations is at least >391,300 (43 * >100 * >91), where 43 is the number of presented

benzimidazole compounds, >100 is the number of chemotherapeutic agents, and >91 is the number of potentiators listed.

Firstly, Agyin explicitly teaches and suggests that the benzimidazoles disclosed therein can be combined with a chemotherapeutic agent and/**or** a potentiator. Appellants' calculation is based on combinations of a benzimidazole compound, chemotherapeutic agent, **and** potentiator. Secondly, because combining chemotherapeutic agents for the treatment of cancer is more than routine in the art of chemotherapy, one skilled in the art would recognize from the disclosure of Agyin that the benzimidazole compounds disclosed therein could be combined with any chemotherapeutic agent or potentiator disclosed therein, including the explicitly disclosed suramin. Appellants argue that the artisan would not know which of the >390,000 combinations to study. This is not persuasive because the skilled artisan would know that any of the explicitly disclosed chemotherapeutic agents and/or potentiator compounds disclosed in Agyin could be studied because this is precisely what Agyin teaches.

XI. Appellants argue that Agyin does not teach using non-cytotoxic suramin as a potentiator because Appellants have shown that the potentiator effect of suramin happens only at low concentrations and does not have sensitization effect at high dose. Appellants further argue that Agyin does not teach how to obtain the narrow concentration range of 10 to 50 μM maintained over 48 hours that would offer the sensitization effect.

In response, the Examiner respectfully submits that the rejection of the claims based on Agyin is directed to the obviousness of formulating a kit comprising a benzimidazole compound of Agyin with suramin with instructions for administration. Agyin need not teach how to obtain

a narrow concentration range of suramin maintained over 48 hours because this is a result of administering suramin and not dependent on the kit.

XII. Appellants argue that Agyin does not teach using kits containing combinations of agents. In support of this argument, Appellants argue that Agyin only proposes kits containing a therapeutically effective amount of a benzimidazole and all other components of the kit are optional.

In response, the Examiner respectfully submits that while Agyin explicitly discloses kits comprising a benzimidazole compound, one skilled in the art would recognize that if used in combination with a chemotherapeutic agent and/or potentiator, the benzimidazole compound should be provided with said a chemotherapeutic agent and/or potentiator for ease of transport, storage, and administration.

XIII. Regarding Tu, Klohs, and Lopez, Appellants again argue that the printed instructions represent new and unobvious findings that cannot be anticipated based on the art regarding dose-calculation of cytotoxic suramin or other drugs. Appellants further argue that Tu, Klohs, or Lopez do not teach the personalized dosing nomogram or the equations of claim 35.

In response, the Examiner respectfully submits that as discussed supra, the cited prior art teaches, suggests, and motivates formulating suramin in a kit with another chemotherapeutic agent and providing instructions for administration. The contents of the instructions are not pertinent to the present rejection(s). Appellants are claiming a product, **not** a method of treatment, method of administration, or method of calculating an amount of suramin to administer to a subject.

XIV. Appellants argue that Tu and Klohs teach the use of suramin as a cytotoxic agent at the maximally tolerated doses that produce toxicity in patients.

The Examiner respectfully submits that it matters not what Tu and Klohs teach regarding the amount of suramin administered because the instant claims are not methods of treatment. Tu and Klohs are provided as evidence that suramin was known in the art to provide a synergistic effect when combined with other chemotherapeutic agents and Klohs explicitly suggests a combination comprising each active ingredient packaged separately, wherein the individually packaged drugs can be placed in a single carton, thereby providing convenience to the attending physician or medical attendant (i.e., a kit).

XV. Appellants argue that Lopez teaches using suramin in a culture flask and does not teach the determination of the suramin dose in a subject.

In response, the Examiner respectfully submits that Lopez, like Tu and Klohs, is relied on for teaching that suramin was known in the art to provide a synergistic effect when combined with other chemotherapeutic agents. Tu, Klohs, and Lopez are not relied upon for their individual teaching, but are rather relied upon for their teachings when combined with other references. In response to Appellants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

XVI. Appellants argue that neither Tu nor Klohs contains the enablement steps to determine the suramin dose that would yield the targeted plasma concentrations effective for producing sensitization.

The Examiner respectfully submits that Tu and Klohs need not teach such determination of suramin doses and need not enable such. The question, as it pertains to the claimed invention and the teachings of the cited prior art, is whether the skilled artisan would have been motivated to provide a kit comprising suramin, a chemotherapeutic agent, and instructions for administration. As set forth in the prior art rejections, the Examiner has established that one skilled in the art is provided with the teaching, suggestion, and motivation to provide suramin in a kit with a chemotherapeutic agent and instructions for administration. Appellants are claiming a product, **not** a method of treatment, method of administration, or method of calculating an amount of suramin to administer to a subject.

XVII. Appellants present several arguments attacking the method that Tu uses to test suramin in subjects. See Brief at page 23.

The Examiner relies on his previous responses regarding the fact that Appellants are claiming a product, **not** a method of treatment, method of administration, or method of calculating an amount of suramin to administer to a subject. The content of Appellants' instructions provided with the claimed product and the method Appellants have established for calculating the amount of suramin to administer to a subject are not pertinent to the present rejections as discussed supra.

XVIII. Appellants further rely on the Declaration of Jessie L.-S. Au, filed March 6, 2008. Declarant opines that the suramin dosing nomogram is needed to ascertain that suramin is used effectively. In support of this opinion, Declarant states, inter alia, that:

a) suramin has been evaluated during the 1980s and 1990s for its antitumor activity in extensive preclinical studies where suramin was administered at doses

that would achieve plasma concentration in excess of 100 μM. Taken together, these studies showed that high doses of suramin did not enhance the efficacy and only enhanced the toxicity of chemotherapy. Dr. Au and collaborators discovered that suramin can enhance the effect of cancer chemotherapy against tumors, and that this suramin effect displays an unusual and counter-intuitive dose-effect relationship in that it occurs only at lower suramin concentration between about 10 to about 50 μM and is lost at higher concentrations. Dr. Au and her co-inventor were awarded USP No. 6,599,912 for the use of low and nontoxic suramin as a sensitizer.

b) Because the effectiveness of suramin is limited to low concentrations and is lost at higher concentrations, clinical application is only practical and achievable if there is a method to identify the proper suramin dose that yields the desired narrow range of concentrations.

c) For most drugs, choosing the proper dose is a relatively routine and easy task. However, this general practice does not apply to suramin, because of its unusual pharmacokinetic behaviors. Dr. Au and collaborators found a substantial inter-subject variability (180%) in the disposition of low and nontoxic doses of suramin in cancer patients, which indicates that administration of the same dose of suramin will not result in the same, desired plasma concentration in all patients.

d) The above considerations indicate the need of a method or composition to take into account the various patient characteristics and the timing of the next treatment relative to the previous treatment, so that the patient is given the proper

dose of suramin. The proper dose is the one that yields the effective concentrations (10-50 μM) and does not yield the higher concentrations that are known to be ineffective.

e) Development of an effective method of administering suramin required extensive research and development in human patients. Dr. Au and collaborators evaluated several methods. The composite findings of these methods were used to develop the suramin dosing nomogram described in the instant application. The nomogram was found to be successful in finding the proper suramin dose to maintain the desired plasma concentrations in 94% of treatment.

f) The dosing nomogram enables a health care professional, such as a pharmacist or a physician, to calculate the suramin dose for a patient using the squared value of the patient's body surface area and the time elapsed since the previous treatment.

g) Absent the dosing nomogram, it will not be possible to calculate the proper suramin dose for a patient and the patient cannot be treated with suramin. For this reason, it is imperative to supply the dosing nomogram together with the drug for clinical treatment of the patient.

h) Alternative methods to determine the needed suramin dose, for example real-time pharmacokinetic monitoring of patient plasma concentrations, are not practical and do not enable the clinical use of suramin in the general population. In other words, the ability to use suramin as a sensitizer in patients relies on using the method of dose calculation or nomogram presented in the instant application.

i) Dr. Au and her collaborators developed the method of dose calculation based on the study of the pharmacokinetics of suramin in patients. Consequently, the method of dose calculation could not exist in the absence of the drug suramin.

j) Based on the foregoing, she comes to the inescapable conclusion that the methods of dose calculation or nomogram cannot exist without suramin, and that suramin cannot exist without the nomogram.

The Examiner previously addressed the contents of the Au Declaration in the Advisory Action mailed 4/9/2008. Briefly, as previously noted by the Examiner, while the Au Declaration would be persuasive with respect to methods of administering suramin in combination with an antineoplastic agent or methods of determining the proper dose of suramin to be administered to a patient, it is not persuasive with respect to the claimed kits for the reasons of record and as discussed supra. The Au Declaration is directed to the non-obviousness of methods of administering suramin and methods of calculating the dose of suramin to administer to a patient. Appellants are claiming a product, **not** a method of treatment, method of administration, or method of calculating an amount of suramin to administer to a subject.

In conclusion, Appellants' arguments and the Au Declaration are predicated on patentable weight being given to the contents of the instructions provided with the claimed kits. It is the Examiner's position that based on established case law, the content of the claimed instructions should not render the claimed invention non-obvious over the prior art. If patentable weight is given to the content of the claimed instructions, it is conceivable that inventors could

patent multiple kits comprising suramin and a chemotherapeutic agent by merely changing the contents of the provided instructions. As stated in In re Ngai, "If we were to adopt Ngai's position, anyone could continue patenting a product indefinitely provided that they add a new instruction sheet to the product. This was not envisioned by Gulack. Ngai is entitled to patent his invention of a new RNA extraction method, and the claims covering that invention were properly allowed. He is not, however, entitled to patent a known product by simply attaching a set of instructions to that product." (Emphasis added).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/James D Anderson/

Primary Examiner, Art Unit 1614

Conferees:

Kathleen K Bragdon

Primary Examiner, TC1600

/Kathleen K Bragdon/

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614